Management of Inflammatory Bowel Disease Across the Lifespan:

Special Considerations for Men, Women, and Children

The second in a series of educational newsletters
based on the proceedings of a roundtable held
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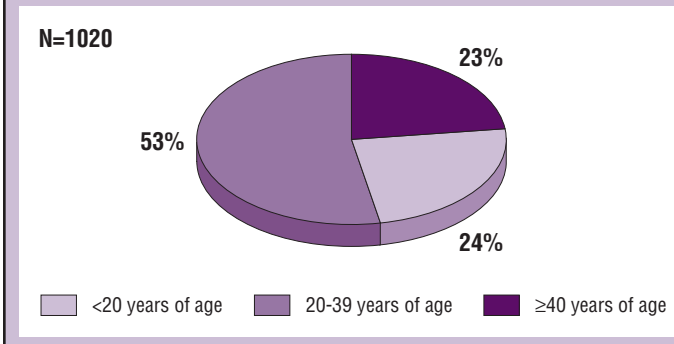
MANAGEMENT OF INFLAMMATORY BOWEL DISEASE ACROSS THE LIFESPAN: SPECIAL CONSIDERATIONS FOR MEN, WOMEN, AND CHILDREN

INTRODUCTION

Inflammatory bowel disease (IBD) comprises two principal disorders, ulcerative colitis (UC) and Crohn's disease (CD). Given its often lifelong course, there is a growing recognition that the management of patients with IBD must encompass not only treatment-related issues, but also the special needs and concerns that arise across the lifespan. For approximately one quarter of patients, these illnesses arise before 20 years of age (Figure 1).[1,2] In fact, the highest age-specific incidence rates occur in early adulthood. At this time of their lives, many young women with IBD will want to start a family and must consider the special needs brought about by their disease.[3] However, there is a second peak incidence that occurs in men and women in their 50s and 60s as well.[4] This newsletter is the second in a series based on a December 2001 roundtable that brought together leading experts and key organizations to review the state of the art in the management of IBD. It highlights the impact of IBD on patients during pregnancy, childhood, and old age. Careful attention to these aspects of care, which are an essential part of the overall management strategy, helps ensure the well-being and quality of life of the many patients who suffer from these chronic inflammatory disorders.

FIGURE 1

AGE AT ONSET OF INFLAMMATORY BOWEL DISEASE



Polito JM II, et al. *Gastroenterology.* 1996;111:580-586.

Watts JM, et al. *Br Med J.* 1966;1:1447-1453.

FERTILITY, PREGNANCY, CHILDBIRTH, AND BREAST-FEEDING

Fertility

Because IBD often arises just as women are planning or preparing to have children, issues related to fertility, pregnancy, childbirth, and breast-feeding may be of particular concern. Women with IBD appear to have a normal chance of becoming pregnant. One study of 147 women with UC who were of childbearing age found that 92% of women who had desired pregnancy had conceived.[5] A second study, which reviewed the reproductive histories of 177 women with CD and 84 women with UC, confirmed that IBD did not reduce fertility.[6] It is evident, however, that more women with IBD are voluntarily childless than are normal controls.

In women with UC who have severe refractory disease requiring surgery, ileal pouch anal anastomosis (IPAA) appears to have a negative effect on fertility. The pre- and postoperative fertility in women with UC who underwent IPAA recently was assessed. Whereas the rate of births before surgery was similar to the expected rate, the birth rate significantly dropped after the operation.[7] Further research has demonstrated that women with UC have relatively normal fecundity that is unaffected by the disease; however, after undergoing IPAA, fecundity is reduced by as much as 80%.[8] Although no formal studies have been performed to test the efficacy of these techniques, some experts suggest that using antiadhesion gels or lifting the ovaries away from the field of surgery and placing them where there is a less likely chance of adhesion formation may help preserve ovarian function. Further discussion of the effects of surgery in IBD occurs later in this newsletter.

Men with IBD have normal fertility, except for those taking sulfasalazine, which causes oligospermia and reduces semen quality.[9,10] The changes in semen quality are reversible within 3 to 4 months after withdrawal of

LEARNING OBJECTIVES

After completing this program, participants will be able to discuss what is known about and be able to summarize current findings and identify knowledge gaps as they apply to the:

- Effect of inflammatory bowel disease (IBD) on fertility, pregnancy, childbirth, and breast-feeding
- Appropriate use of medical therapy during pregnancy and breast-feeding
- Psychosocial issues in patients with IBD
- Special considerations for the evaluation, treatment, and overall management of children and adolescents
- Issues and concerns specific to the management of elderly patients with IBD

Target audience: US and Canadian gastroenterologists and fellows

sulfasalazine and placement on a sulfa-free 5-aminosalicylic acid (5-ASA) agent to control disease activity.[11]

Pregnancy

Pregnancy in patients with IBD has been evaluated from a dual perspective: the effect pregnancy has on disease as well as the effect the disease has on pregnancy and the developing fetus. Regarding the effect of pregnancy on disease, one study found that about one third of women with quiescent UC suffered a relapse during the 12 months of gestation and puerperium—a rate similar to that of nonpregnant patients for the same time period.[12] In women with active UC at the time of conception, approximately 45% got worse, 25% improved, and 25% remained the same.[12] Women with quiescent CD were shown to relapse during pregnancy and puerperium in about 25% of cases, roughly the same percentage expected for nonpregnant women. Active CD was shown to improve in one third of pregnant patients, whereas in one third it remained unchanged and in the final third it worsened.[12]

In addition, it has been shown that the nutritional status of the patient may have long-term implications for the course of IBD, particularly for patients with CD. Women with CD who had a normal nutritional status at the time of conception had fewer relapses in the 3 years after pregnancy than did malnourished patients.[13] Therefore, maintenance of a normal nutritional status is an important goal in pregnancy.

Numerous studies have shown that IBD has relatively little effect on pregnancy overall, and it does not pose a threat to the developing fetus. In a controlled study of 82 pregnancies, neither CD nor UC had a major effect on duration of pregnancy, mode of delivery, hypertension, and/or proteinuria, although the birth weight of babies born to women with CD was lower.[14] A more recent prospective case-controlled study of 30 pregnancies in patients with either UC or CD similarly found that disease did not influence the outcome of pregnancy.[15] Women should be advised to conceive when in remission, if possible. In active disease, there may be a slightly increased risk of spontaneous abortion or stillbirth.[12]

Women with IBD have an increased risk of preterm birth (<37 weeks). Baird and coworkers reported a two- to threefold increase in preterm births in their study.[6] Recent research by Dominitz and colleagues has shown that births to women with CD were more likely to be preterm, have low birth weights, and be small for gestational age.[16] Babies born to mothers with UC were at greater risk for congenital abnormalities. Such information suggests that close obstetric monitoring during the last trimester is warranted. There is no convincing evidence that vaginal delivery is either safe or harmful for women with IBD, and vaginal delivery should be considered for all women without active perineal disease. In one series, vaginal delivery was said to be safe after IPAA.[17] However, delivery mode should be individualized for each patient depending on the size of the fetus and the number of future pregnancies.

Medical Therapy During Pregnancy

The goals of IBD treatment are essentially the same during pregnancy: the maintenance of disease remission and treatment of relapse. The Food and Drug Administration (FDA) drug classification of agents used in IBD is presented in Table 1.

TABLE 1

FOOD AND DRUG ADMINISTRATION CLASSIFICATION OF DRUGS FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE IN PREGNANCY

Category A	Category B	Category C	Category D	Category X
N/A	Mesalamine Sulfasalazine Corticosteroids Metronidazole[†] Infliximab	Ciprofloxacin Cyclosporine	Azathioprine 6-Mercaptopurine	Methotrexate

*Category definitions:

A: Controlled studies in women do not show a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote.

B: Animal studies do not show a risk to the fetus and there are no controlled studies in pregnant women, or animal studies do indicate a fetal risk but controlled studies in pregnant women do not.

C: Either animal studies show a fetal risk and there are no controlled studies in women or there are no available studies in women or animals.

D: There is positive evidence of fetal risk, but there may be certain situations in which benefit may outweigh the risk.

X: There is definite fetal risk based on studies in animals or humans, or based on human experience. The risk clearly outweighs any benefit in pregnant women.

[†]Safe if used after the first trimester.

Briggs GG, et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.* 5th ed. Baltimore, Md: Lippincott Williams & Wilkins; 1998. Remicade® (infliximab). *Physicians' Desk Reference®.* 55th ed. Montvale, NJ: Medical Economics Co; 2000:1085-1088.

Management of Inflammatory Bowel Disease Across the Lifespan: Special Considerations for Men, Women, and Children, as published in this *Clinical Courier®*, is the second in a series of newsletters based, in part, on the proceedings of a roundtable that was held on December 12-13, 2001, in Washington, DC. Learning objectives of that roundtable were as follows:

By the end of the program, participants were able to discuss what is known about sex differences and were able to summarize current findings and identify knowledge gaps as they apply to the:

- Epidemiology and proposed etiologies of ulcerative colitis and Crohn's disease
- Clinical and diagnostic findings in adults and children with IBD
- Clinical utility of traditional and evolving therapies in the everyday management of ulcerative colitis and Crohn's disease
- Psychosocial challenges IBD patients face
- Relationship between adherence and disease relapse to optimize adherence in clinical practice

Statement of Need: Strategies for the management of IBD are continuing to evolve as the result of research advances, growing clinical experience, and an expanding therapeutic armamentarium. This progress is paving the way toward more efficient approaches to the differential diagnosis of IBD as well as more effective methods of establishing and maintaining remission. Unique treatment considerations in special populations such as women, children and adolescents, and the elderly are also gaining greater recognition. An appreciation of these ongoing developments is crucial to optimizing therapeutic responses, reducing the risk of complications, and improving the quality of life for the approximately one million Americans who suffer from IBD. Awareness of these issues will help physicians become better equipped to meet the challenges of IBD in daily clinical practice and will support the practice of evidence-based medicine.

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Category A Drugs

Category A drugs are those agents that pose no fetal risk as demonstrated in controlled human studies. This category includes mainly vitamins and supplements, but few prescription medications. The safest of prescription drugs generally are found in category B. Lack of agents in this category may reflect both the practical limitations of conducting studies in pregnant patients and previous guidelines that limited the participation of women in early studies. FDA guidelines from 1977 to 1993 prohibited the inclusion of women of childbearing age in the early phases of research studies unless the woman had a life-threatening disease.[18] More recent guidelines, however, have encouraged the participation of women in all phases of drug development, and recent evidence suggests that women are participating in new clinical trials in approximately the same proportions as men.[18] Still, it is clear that more studies are needed to establish the safety and efficacy of drugs both for women during pregnancy and for the children they carry.

Category B Drugs

Mesalamine is safe to use in pregnancy. Patients should be maintained on the same dose to prevent relapse. In a study of 165 women, of whom 72% were exposed throughout pregnancy, mesalamine use was not associated with an increase in malformations.[19] Major malformations occurred in 0.8% of infants of treated women in comparison with 3.8% of infants in a control group. There were no significant differences between groups in the maternal obstetric history, rates of live births, miscarriages, pregnancy terminations, ectopic pregnancies, delivery method, or fetal distress. In this study, 20% of women were taking a mean daily dose of 2.4 to 3.2 g and another 20% were taking daily doses ≥3.2 g.[19] As there are, historically, few studies conducted in pregnant women, these data offer promise that higher doses of mesalamine for treating women with UC during pregnancy appear to be safe. Induction doses of 4.8 g/day have been shown to be safe and effective in nonpregnant patients, and such patients should be maintained on this dose to maintain remission. Indeed, maintenance of remission is an important goal during pregnancy, as quiescent disease is associated with the birth of neonates of higher gestational age.[19]

Sulfasalazine also is a category B agent. Although safe, frequent side effects may hamper use.[12] Because it interferes with folic acid absorption,[10] folic acid supplementation prior to conception and during pregnancy is required. In addition, sulfasalazine has a negative, but reversible, effect on male fertility. Men who wish to conceive with their partners should be switched to other 5-ASA preparations, such as mesalamine, that do not affect sperm quality.[10]

Corticosteroids apparently pose little risk to the fetus. Although some reports have suggested an increase in stillbirth or a reduction in birth weight with corticosteroid use, the majority of reports have been reassuring.[12]

Metronidazole readily crosses the placental barrier, and its use in pregnancy is controversial because it is carcinogenic in rodents. The risk:benefit ratio must be carefully weighed.[20] Although there are no well-controlled trials in pregnant women, its safety in pregnancy was assessed through a meta-analysis.[21] In 1083 exposed women, metronidazole did not appear to be associated with an increased teratogenic risk.[21] However, because of overall conflicting evidence and lack of long-term data, metronidazole should be used with caution during the first trimester.[20,22]

Because of lack of data, infliximab treatment should be stopped 3 months before conception until further information on its effects during pregnancy is known.

Category C Drugs

The effects of ciprofloxacin in pregnancy were reported in a study involving 103 women, of whom 89 were exposed to treatment during the first trimester. There were 63 normal births, 18 therapeutic abortions, 10 spontaneous abortions, 8 congenital abnormalities, and 4 fetal deaths in utero.[23] Although the report notes that ciprofloxacin has been used frequently in pregnancy without causing adverse events, these data suggest that it should not be administered unless there is significant need for its use.[20]

Based on a relatively small number of reports, cyclosporine apparently does not pose a major risk to the fetus.[20]

Faculty members are required to inform the audience when they are discussing off-label or unapproved uses of devices or drugs. Devices or drugs that are still undergoing clinical trials are identified as such and should not be portrayed as standard, accepted therapy. Please consult full prescribing information before using any product mentioned in the program. If using products in an investigational, off-label manner, it is the responsibility of the prescribing physician to monitor the medical literature to determine recommended dosages and use of the drugs.

UNAPPROVED/INVESTIGATIONAL USE

Generic Name	Trade Name	Approved Use (if any)	Unapproved/ Investigational Use
Azathioprine (derivative of 6-mercaptopurine)	Imuran®	Rheumatoid arthritis and renal transplantation	Crohn's disease and ulcerative colitis
Ciprofloxacin	Cipro®	Various aerobic bacterial infections	Crohn's disease
Cyclosporine	Sandimmune®; Neoral®	Allogeneic transplantation, rheumatoid arthritis, and psoriasis	Crohn's disease and ulcerative colitis
5-Aminosalicylate mesalamine	Asacol®; Pentasa®; Rowasa®; Canasa®	Ulcerative colitis	Crohn's disease
olsalazine sodium	Dipentum®		
balsalazide disodium	Colazal™		
Glucocorticoids (hydrocortisone, prednisone, and prednisolone)	Various	Ulcerative colitis and numerous other indications	N/A
Infliximab (anti-TNF-α monoclonal antibody)	Remicade®	Moderately to severely active Crohn's disease refractory to conventional treatments, fistulizing Crohn's disease, and rheumatoid arthritis	Ulcerative colitis and other inflammatory disorders
Methotrexate	Various	Neoplastic disease, psoriasis, and rheumatoid arthritis	Crohn's disease
6-Mercaptopurine	Purinethol®	Chemotherapy, leukemia, and transplantation	Crohn's disease and ulcerative colitis
Metronidazole	Flagyl®	Trichomoniasis *(Trichomonas vaginalis),* amebiasis, and anaerobic bacterial infections	Crohn's disease
Sulfasalazine	Azulfidine®	Ulcerative colitis	Crohn's disease

TNF=tumor necrosis factor; N/A=not available.

Category D Drugs

Azathioprine (AZA) and 6-mercaptopurine (6-MP) appear to be relatively safe in pregnancy, although both are category D drugs. The safety of AZA in pregnancy in IBD was assessed in a small retrospective study involving 14 patients.[24] No congenital abnormalities or subsequent health problems were noted. The safety of 6-MP in childbearing patients was evaluated in a case-controlled study among 155 subjects who had been exposed to 6-MP.[25] Subjects included patients who conceived after stopping 6-MP, patients who conceived while taking 6-MP and stopped during pregnancy, patients who conceived while taking 6-MP and continued through pregnancy, and patients who conceived prior to ever taking 6-MP. Its use was not associated with increased prematurity, spontaneous abortion, congenital abnormalities, or childhood infections or neoplasia.

Category X Drugs

Methotrexate is contraindicated during pregnancy. Its use is associated with fetal abnormalities, and the potential risks of the drug outweigh its benefits.[20]

Breast-feeding

Medical Therapy When Breast-feeding

Some IBD medications are safe to use in breast-feeding when indicated. Mesalamine, sulfasalazine, and corticosteroids appear to be safe. There are few available data on the use of AZA/6-MP. The use of ciprofloxacin is not recommended, and metronidazole should be used with caution. Methotrexate and cyclosporine are contraindicated in nursing mothers.[20]

PSYCHOSOCIAL ISSUES

There is increasing appreciation that the psychosocial aspects of illness have an important impact on overall health in patients with IBD. Recent attention has focused on measuring the quality of life of patients, as well as a better understanding of their concerns. This section reviews three important areas: the quality of life in patients with IBD, their health-related concerns, and the impact of IBD on sexual activity. Knowledge of how disease- and non–disease-related factors play a role in patient well-being can help identify patients who may benefit from psychosocial intervention.

Quality of Life

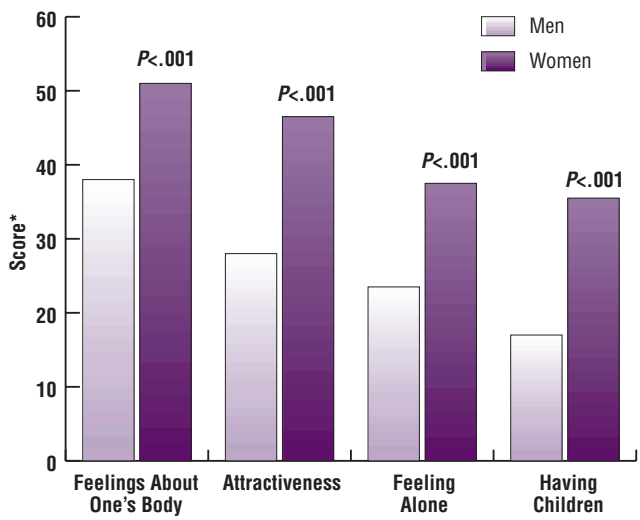
Patients with IBD, in general, are shown to have impaired health-related quality of life. The most important predictors of poorer health-related quality of life are the extent and severity of disease and the efficacy of treatment. Quality of life in patients with IBD is also significantly impacted by several non–disease-related factors such as unemployment, a lower level of education, an important life event in the prior 12 months (such as job loss, divorce, separation, or death in the family), female gender, prior use of corticosteroids, and prior use of immunomodulators.[26] In a study among patients on home parenteral nutrition (who usually represent the most ill patients), the health status profile was relatively good for younger patients, but poorer for those older than 55 years of age.[27] Thus, increasing age also can negatively impact quality of life.

Health-Related Concerns in IBD

The worries and concerns of patients with IBD have been measured in several studies. Drossman, using an IBD-specific questionnaire, identified four indices of disease of greatest concern: impact of disease (being a burden, loss of energy, loss of bowel control), sexual intimacy, complications (development of cancer), and body stigma (feeling dirty or smelly).[28] A higher level of concern was found among women, among patients with greater disease severity, and among those of lower educational status. A recently published study by Maunder and colleagues has provided further insight in the influence of gender on illness-related concerns.[29] Women were significantly more likely to report a higher severity of IBD symptoms and a higher level of overall concern about IBD than men, particularly regarding four illness-related factors: having children, attractiveness, feelings about one's body, and feeling alone.[29] Figure 2 shows the mean scores for men and women for these items on the Rating Form of IBD Patient Concerns questionnaire. Further, an interaction was found between disease and gender regarding sexual performance and intimacy, particularly in CD. Compared to men with CD, women report a much higher level of concern for these two aspects of disease.[29] These data provide an increased appreciation that gender differences contribute significantly to the experience of disease. They also highlight the need for physicians to be aware of interpersonal concerns, provide empathetic support, and suggest psychosocial intervention when necessary.

FIGURE 2

INFLAMMATORY BOWEL DISEASE CONCERNS THAT DIFFER BY GENDER



Mean scores on the Rating Form of IBD Patient Concerns questionnaire; higher scores for each item (0 to 100) indicate a greater degree of concern.

Maunder R, et al. *Can J Gastroenterol.* 1999;13:728-732.

Impact of IBD on Sexual Activity

The presence of sexual problems has been assessed in women with CD. Women with CD reported significantly more sexual problems, primarily less frequent or no intercourse, than did women without CD ($P<.005$).[30] Dyspareunia, abdominal pain, diarrhea, and fear of fecal incontinence during intercourse were reasons for reduced sexual activity. In contrast, a larger postal survey in women with UC and men with UC or CD found no significant differences in the overall frequency of sexual intercourse in comparison with 122 controls.[30] Even so, survey responders reported that fear of fecal incontinence, tiredness, abdominal pain, and need for proximity to the toilet limited sexual activity.

Most patients with IBD can function well sexually and are relatively active, although many will require intermittent intense support and care. The presence of a strong social support network and of positive coping

strategies is important. Support for patients is offered through the Crohn's & Colitis Foundation of America (www.ccfa.org).

COMORBID CONDITIONS

Comorbid conditions in patients with IBD can complicate patient management and increase the overall negative impact of disease. A number of comorbid conditions, including psychiatric factors, irritable bowel syndrome (IBS), and endometriosis can play a role. In addition, fluctuations associated with the menstrual cycle can impact IBD symptoms.

Depression and/or anxiety are present in a significantly higher percentage of patients with UC and CD than in control subjects ($P<.05$ for both).[31] Depression and anxiety are associated with physical morbidity and correlate with malnutrition and lower health-related quality of life scores.[31,32]

Many patients with IBD also may suffer from IBS.[33] The coexistence of IBS can confound the diagnosis and cause confusion over symptomatology. Women tend to report higher levels of IBS symptoms, so gender-related differences also may add to the overall impact of disease in patients with concomitant IBD and IBS.[34] In addition, some IBD treatments may aggravate IBS. For example, some patients with UC and IBS may have difficulty with ileoanal anastomoses, due to relatively more bowel movements or painful spasms when the ileal pouch is distended. Or, knowledge that a patient with CD also has IBS may help in the evaluation of postoperative diarrhea and left-sided pain after bowel resection. The concept that IBS and IBD can coexist is helpful in evaluating and advising patients with IBD.[33]

Intestinal endometriosis can mimic IBD, and it should be considered in the differential diagnosis of recurring lower abdominal pain and other episodic bowel symptoms in women of childbearing age.[35] Endometriosis can also coexist with IBD. Craninx and colleagues reported a series of eight surgical candidates with CD who were found to have endometriosis upon histologic examination.[36] None was suspected to have endometriosis based on previous gynecologic or radiologic tests.

Finally, a relationship has been observed between the menstrual cycle and bowel function in patients with IBD and/or IBS. Premenstrual and menstrual symptoms are reported more frequently by women with IBD and/or IBS. Bowel habits change and disease symptoms increase during this time. Changing or increasing levels of progesterone and/or increased prostaglandin production have been proposed to explain these findings. The physiologic and clinical effects due to the menstrual cycle are important when evaluating bowel symptoms in menstruating women. Cyclic alterations in symptoms should be considered when contemplating changes in treatment and in evaluating their efficacy.[37]

THE IMPACT OF SURGERY

Often, both the patient and the gastroenterologist view IBD surgery as a "failure." Instead, it should be seen as the best means, in combination with pre- and postoperative medical therapy, for achieving optimal health and quality of life. Gastroenterologists and surgeons have an important role to play before surgery takes place, weighing the benefits and risks, involving patients in the decision-making process, preoperative teaching, and outlining realistic outcomes. Issues related to age, occupation, and gender should be thoroughly discussed, and the type of surgery should be chosen to best meet the needs of individual patients. It must be recognized that the processes of surgery, recovery, and adjustment themselves profoundly impact patients.[38]

TABLE 2

REPORTED INCIDENCE OF POSTOPERATIVE SEXUAL DYSFUNCTION

	1 Year After IPAA		12 Years After IPAA	
	Men (n=762)	Women (n=692)	Men (n=215)	Women (n=198)
Sexual dysfunction present after IPAA	1%	8%*	2%	11%†

IPAA=ileal pouch anal anastomosis.

*P=.04.
†P=.03.

Reprinted with permission from Farouk R, Pemberton JH, Wolff BG, Dozois RR, Browning S, Larson D. Functional outcomes after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Ann Surg.* 2000;231(6):919-926.

Long-term outcomes after IPAA recently have been assessed. In one study, overall long-term quality of life was excellent and the level of continence was satisfactory after stapled ileal pouch surgery.[39] A second study evaluated outcomes specifically regarding patient sex, childbirth, and age.[40] Functional outcomes were comparable between men and women, but incontinence rates were higher in older than younger patients. Eighty-five of 546 women had a pregnancy and vaginal delivery after IPAA; childbirth did not adversely affect pouch function. After IPAA, 25% of patients reported improvements in sexual activity, whereas approximately half (56%) reported no change. Among the 19% of patients who reported restricted sexual activity after surgery, most were women. Sexual dysfunction among men and women 1 year and 12 years after IPAA is presented in Table 2. Men reported retrograde or no ejaculation and women reported dyspareunia and fecal incontinence during intercourse.[40] The finding that most sexual dysfunction is observed among women suggests that preoperative counseling and contact with other patients of the same sex and age who have undergone such surgery may be helpful.

SPECIAL CONSIDERATIONS IN CHILDREN AND ADOLESCENTS

IBD often occurs at a particularly vulnerable period of childhood and adolescence, with potentially adverse effects on growth, quality of life, and psychosocial functioning. Although there are many common clinical features and therapeutic options are similar, the diagnosis and management of IBD in pediatric patients often present unique clinical challenges.

Diagnostic Dilemmas

The unique presentations of IBD in children include recurrent "IBS-like" abdominal pain, growth failure, delayed puberty, anorexia nervosa, juvenile arthritis, and fever of unknown origin.[41] In its milder forms, the nonspecific symptoms of IBD may easily be mistaken for recurrent abdominal pain or another functional bowel disorder. Delayed diagnosis may be the result, particularly in CD, in which anorexia, growth failure, arthralgias, or fever may be present in the absence of any gastrointestinal symptoms. In contrast, in most cases of UC, hematochezia generally leads to rapid consultation and a diagnostic colonoscopy. Symptoms of IBD are often nonspecific, and diagnostic tests are often invasive. Consequently, there is a clinical need for accurate, noninvasive screening for IBD, particularly for the pediatric patient population. Recent data in pediatric patients suggest that serologic testing for the perinuclear antineutrophil cytoplasmic antibody (pANCA) and the anti–*Saccharomyces cervisiae* antibody (ASCA)

can be useful for screening for possible IBD in patients with nonspecific symptoms and normal physical exams.[42] If clinical suspicion for IBD is low, the clinical workup should assure a normal physical exam, exclude perianal disease, and verify normal growth velocity. Limited initial testing (complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum albumin, iron, and serologic assays for pANCA and ASCA) should be performed. If the clinical suspicion is high, a complete diagnostic workup is needed.

Monitoring Disease Activity

The invasiveness of procedures used for monitoring IBD disease activity, such as endoscopy, has driven the search for techniques better accepted in children. Pediatric patients with CD, in particular, often manifest few symptoms, yet commonly are found to have anorexia and growth failure. In such patients, the ability to detect subclinical inflammation would be of great benefit. One such technique is pulsed color Doppler abdominal ultrasound, which is based on the finding that active CD is associated with neovascularization. Spalinger and colleagues used this approach to estimate intestinal wall vessel density as a function of disease activity.[43] Affected bowel loops were found to be significantly thicker in pediatric patients with active CD than in those whose disease was in remission ($P<.001$). Vessel density was more frequently moderate or high in active CD than in quiescent CD. This noninvasive technique is simple to perform in young patients and has the potential advantage of allowing sequential monitoring of disease. Barium small-bowel series with late films of the colon are often revealing, are noninvasive, and are well tolerated by adolescents.

Growth and Nutritional Issues

Impaired nutritional status in children and adolescents with IBD can cause abnormally slow growth, which can result in permanent short stature and delayed sexual maturation. Chronic deficient energy and protein intake is of particular concern in patients with CD, nearly half of whom have growth failure.[44] In a review of records from adult patients who were diagnosed with IBD in childhood or adolescence, 31% (15/48) had permanent height deficits.[45] In patients with growth delay, elemental diets have been used successfully to increase growth velocity, improve disease activity, and reduce corticosteroid requirements.[46,47] The available data support the use of enteral nutritional treatment to induce remission in patients with CD, even if its efficacy does not equal that of corticosteroids.[48] The major advantages of this approach are the virtual absence of side effects, avoidance of corticosteroid therapies that stunt growth, and nutritional repletion.[48] However, not all patients with CD are candidates for nutritional management. Patients with extensive or distal colonic involvement or who have severe anorectal disease often do not respond well. Further disadvantages include low acceptability of taste and the relatively high cost of diet therapy compared with most medications.

Children with IBD have decreased bone mineral density (BMD), which has significant implications for morbidity both in childhood and in adult life. It occurs to a greater extent in patients with CD.[49] Some authors have recommended that all children with CD have BMD determinations every 2 years. Patients at high risk (eg, those with malnutrition, growth failure, or intestinal resection) should be screened annually. Particular attention should be paid to the treatment of pediatric patients using corticosteroids to induce disease remission, because of the known adverse effects of these agents on BMD. In patients with low BMD or other risk factors, (eg, female, Caucasian, Asian, family history of osteoporosis), nutritional therapy should be considered, and corticosteroid therapy should be avoided.[50]

Growth failure and pubertal delay are common and serious complications of pediatric IBD. Early and aggressive treatment to control disease, which typically includes medical management and nutritional supplementation, is needed to restore normal body composition and reverse weight deficit and linear growth failure.

TABLE 3

PERCENTAGE OF PEDIATRIC PATIENTS TAKING MESALAMINE AND SULFASALAZINE EXPERIENCING DIFFICULTIES WITH ORAL ADMINISTRATION OF MEDICATION

	Mesalamine* (n=22)	Sulfasalazine (n=45)
Dissatisfied with tablet size	18%	31%
Tablet size interfering with regular medication	14%	13%
Better compliance if tablet smaller	14%	7%
Problem in frequency of dosing	9%	29%
Decreased frequency of dosing would be helpful	5%	60%
Missing/forgetting doses	3%	47%

*Asacol®.

Adapted with permission from Barden L, et al. *Aliment Pharmacol Ther.* 1989:3:597-603.

Medical Management

The medical therapy for IBD in children and adolescents is similar to that in adults. Aminosalicylates are first-line therapy. A pediatric IBD study examined the occurrence and tolerance of side effects during treatment with mesalamine (Asacol®) and sulfasalazine.[51] Patients in the sulfasalazine group received dosages ranging from 250 mg tid to 1000 mg qid. The usual Asacol® dosage was 400 mg bid, but dosages ranged from 400 mg qd to 800 mg bid. The results demonstrated that although the majority of patients were maintained in remission with either drug, patients reported a preference for Asacol® based on ease and frequency of administration (Table 3). No serious adverse events occurred in patients treated with Asacol®, and there were fewer side effects with Asacol® than with sulfasalazine. The fact that mesalamine treatment is safe and well tolerated is notable, because pediatric doses are relatively higher on a gram-per-day basis than those taken by adults. As is the current standard of therapy in adults, the dose of mesalamine should be the same for both induction and maintenance of remission.

The safety and efficacy of olsalazine and sulfasalazine in pediatric patients also have been compared.[52] Side effects in both groups were frequent. After 3 months, 39% (11/28 patients) taking olsalazine were asymptomatic or clinically improved compared with 79% (22/28 patients) taking sulfasalazine. In addition, 10 patients on olsalazine, compared to one on sulfasalazine, required prednisone because of lack of response or worsening colitis.[52]

Corticosteroids have significantly different side effects in the pediatric population. Use of corticosteroids in children is associated with adverse events, including delayed growth and pubertal development. Long-term administration of corticosteroids can cause substantial delays in height gain. In most patients, these negative effects on height are added to the negative effects of malnutrition.

AZA and 6-MP are effective immunomodulatory drugs for the long-term management of both UC and CD. A recent randomized, placebo-controlled trial in 55 pediatric patients with active CD showed that the addition of 6-MP 1.5 mg/kg/day to the regimen significantly decreased the

need for prednisone and improved maintenance of remission ($P<.01$ and $P=.007$, respectively).[53] This study supports the use of AZA or 6-MP in pediatric patients with moderate to severe CD to improve the natural history of the disease, to effectively maintain long-term remission, and to prevent corticosteroid dependence or resistance. Despite the therapeutic advantages of AZA and 6-MP, unfounded concerns regarding drug-related toxicity and delayed onset of action have restricted their use in IBD.[53]

Psychosocial Issues

The psychosocial impact of IBD may be even more significant in children than it is in adults. Although the mortality is low, IBD nevertheless presents a major, lifelong health threat, challenging the psychological resources of both the affected child and the family. IBD frequently interferes with physical activities, limits social interactions, disrupts education, impairs growth, and delays puberty. Children with IBD have been reported to have substantially impaired quality of life.[54] They fear everyday childhood activities and are concerned for their future. These children need sympathetic management, and efforts should be concentrated on improving their daily psychosocial functioning so that their lives are as normal as possible.[55] This can best be achieved by medically controlling disease activity, achieving normal growth and development through nutritional interventions, and providing psychosocial support to patients and their families.

SPECIAL CONSIDERATIONS IN ELDERLY PATIENTS

Although most cases of IBD develop during the second and third decades of life, there is a clear bimodal distribution in the pattern of onset, with a second peak occurring in the fifth and sixth decades of life.[4] As the population ages overall, the number of elderly patients with IBD will continue to increase because of the lifelong nature of the disease, better therapy, and new-onset cases.

The clinical manifestations and course of IBD in the elderly are similar to those seen in the younger population, although in UC there is a trend toward more distal disease and in CD colonic involvement is more common than small-bowel disease.[2,56] In addition, whereas mortality rates in UC and CD are generally similar to those of age-matched controls, a subset of elderly patients with UC will have a severe initial attack that may be associated with a high mortality rate.[57] Features of IBD in the elderly are presented in Table 4.[57] Conditions that can mimic IBD in the elderly, which must be included in the differential diagnosis, are ischemic colitis, infectious colitis, diverticular disease, collagenous and microscopic colitis, radiation enterocolitis, medication-induced colitis (particularly nonsteroidal anti-inflammatory drugs), and malignancy.[57] The presence of comorbid disease and the broad differential diagnosis of colitis in the elderly may make the definitive diagnosis of IBD more challenging.

Medical and surgical options are similar to those for younger age groups, although the management of elderly patients with IBD is made more challenging by the high frequency of concomitant medical problems and overall health status. This highlights the need for therapies, such as mesalamine, that are known to be safe. In addition, special care must be taken to avoid glucocorticoid therapy, not only because of the increased risk of osteoporosis, but because such therapy can exacerbate concomitant conditions such as diabetes, hypertension, and congestive heart failure.[57] The indications for surgery and the choice of operations in elderly patients are similar to those in persons of younger age. However, the surgical procedures must be chosen with the needs of individual patients in mind. For example, poor sphincter tone resulting in higher rates of fecal incontinence may make IPAA a less attractive option for elderly patients with UC.[57]

TABLE 4

FEATURES OF INFLAMMATORY BOWEL DISEASE IN THE ELDERLY

Ulcerative Colitis

- Slight male predominance
- Severe initial attacks
- High mortality rates with severe attacks
- More frequent distal disease
- Possibly lower rates of relapse and extension
- Low risk of colorectal cancer
- Good long-term prognosis

Crohn's Disease

- Slight female predominance
- Delays in diagnosis
- More frequent colonic and less frequent ileal involvement
- More frequent distal colonic involvement, with good response to medical therapy
- Low recurrence rates
- Low mortality rates, particularly with distal colonic involvement

Adapted with permission from Grimm IS, Friedman LS. *Gastroenterol Clin North Am.* 1990;19:361-389.

CONCLUSION

IBD is a chronic, often lifelong disorder. Although factors such as the severity of illness and the efficacy of treatment have the greatest influence on quality of life, many non–disease-related factors, including gender and comorbid illness, also play a role. Further, certain issues—fertility, pregnancy, and specific illness-related concerns—may be of greater importance for women than men. Recognition of the unique impact of gender, and of the special considerations in children and elderly patients, is necessary for all physicians. A comprehensive approach, one that addresses the many dimensions of IBD, will ensure the best possible care for all patients.

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MANAGEMENT OF INFLAMMATORY BOWEL DISEASE ACROSS THE LIFESPAN: SPECIAL CONSIDERATIONS FOR MEN, WOMEN, AND CHILDREN 2nd in a Series of 3 Newsletters

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1. Which of the following statements is true regarding the onset of inflammatory bowel disease (IBD)?
   a. For approximately 15% of patients, the disease begins before 20 years of age.
   b. Approximately one quarter of patients will have IBD by 20 years of age, and the peak onset is in early adulthood.
   c. There is a bimodal distribution in the pattern of onset, with the majority of cases beginning in the fifth and sixth decades of life.
   d. For most patients, IBD begins in early childhood and is a chronic, lifelong disease.
2. Which of the following statements accurately describes the fertility of patients with IBD?
   a. Although the overall fertility of women with IBD is normal, more women with IBD choose to be childless than do their normal peers.
   b. Men with IBD have subnormal fertility because of retrograde or no ejaculation.
   c. Women with quiescent ulcerative colitis (UC) or Crohn's disease (CD) have normal fertility, whereas those with active disease are not fertile.
   d. Ileal pouch anal anastomosis (IPAA) apparently has little effect on the ability of women to conceive.
3. Choose the following statement that best describes medical therapy in pregnant patients with IBD:
   a. Because the risks to the fetus of most IBD medications outweigh the benefits, medical therapy should be stopped in pregnant patients.
   b. Because few women with quiescent disease will experience a relapse, it is safe to taper medical therapy during pregnancy.
   c. Because of the lack of data on the teratogenicity of aminosalicylates, patients wishing to conceive should be switched to corticosteroids.
   d. Mesalamine is safe to use during pregnancy, and patients should be continued on the same dose to maintain remission and prevent relapse.
4. Which of the following disease-related factors is known to impact the quality of life of patients with IBD?
   a. Gender
   b. Lower socioeconomic status
   c. Extent and severity of disease
   d. Ability to have children
5. Which of the following is not an aspect of IBD of more concern to women than men?
   a. Developing cancer
   b. Feeling alone
   c. Attractiveness
   d. Feelings about one's body
   e. Having children
6. Recent studies assessing the outcome of IPAA have found that:
   a. More men than women have sexual dysfunction 1 and 12 years after surgery.
   b. Functional outcomes and rates of incontinence were not impacted by the age and sex of patients.
   c. Most patients continue to report sexual dysfunction after IPAA.
   d. Vaginal delivery after IPAA is safe.
7. Why is it more difficult to diagnosis IBD in pediatric patients?
   a. Children with UC often have a delayed diagnosis because of nonspecific symptoms.
   b. Serologic testing is not accurate in children.
   c. Children more frequently have gastrointestinal symptoms of IBD than extraintestinal manifestations.
   d. Children with IBD have unique presentations, including growth failure, delayed puberty, and fever of unknown origin.
8. Which of the following statements is not accurate regarding medical therapy in children?
   a. Use of corticosteroids in children does not cause delayed growth and pubertal development.
   b. Mesalamine is safe and effective therapy in children with IBD.
   c. A recent study supports the use of azathioprine and 6-mercaptopurine in children with moderate to severe CD.
   d. Enteral nutritional treatment is effective for inducing remission in patients with CD.
9. The clinical manifestations of IBD in the elderly are similar to those in younger patients except that:
   a. Elderly patients with UC have more distal disease.
   b. Elderly patients with UC have low recurrence rates and low mortality rates.
   c. Elderly patients with CD commonly have more colonic involvement than small-bowel disease.
   d. a and c
   e. All of the above
10. Why is the management of elderly patients more challenging than that of younger patients?
    a. Comorbid conditions in elderly patients complicate management.
    b. Elderly patients are not suitable surgical candidates.
    c. The unique clinical manifestations and course of IBD in the elderly make it difficult to reach a correct diagnosis.
    d. Medical options for elderly patients are different than those for younger patients.

Please record your posttest answers: 1. ____2. ____3. ____4. ____5. ____6. ____7. ____8. ____9. ____10. ____

Evaluation

We hope this newsletter has provided information that will be useful in your practice. Your evaluation will help us plan future programs. May we have your comments?

Please evaluate the newsletter contents by circling your response.

1. How would you rate:	Superior	Excellent	Good	Fair	Poor
a. Value of the topic	5	4	3	2	1
b. Relevance to your practice	5	4	3	2	1
c. Organization of newsletter	5	4	3	2	1
d. Newsletter length	5	4	3	2	1
e. Quality of information	5	4	3	2	1

2. Did this material succeed in meeting its educational objectives?
   ❑ Yes ❑ No
   Please explain: _____

3. Will reading this newsletter change the way in which you manage patients?
   ❑ Yes ❑ No
   Please be as specific as possible: _____

4. Do you believe the newsletter contained pharmaceutical industry bias?
   ❑ Yes ❑ No
   Comments: _____

5. How do you prefer to receive continuing medical education information? (On a scale of 5 to 1, please score each of the following: 5 = very useful; 3 = somewhat useful; 1 = don't use)
   _____ a. Newsletter
   _____ b. Video
   _____ c. Audiotape
   _____ d. Teleconference
   _____ e. Monograph/Journal Supplement
   _____ f. Symposium/Conference
   _____ g. CD-ROM/Computer Based
   _____ h. Webcast

6. Do you believe such materials, sponsored by educational grants from industry, are:
   _____ 10 very appropriate/useful, 0 not appropriate/useful?

7. Actual amount of time I spent in this activity: _____ hours(s)

Name (please print) _____ Degree _____

Specialty _____

Address _____

City _____ State _____ ZIP _____

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